Remarks/Arguments

The foregoing amendments in the claims are fully supported by the specification as originally filed, and do not add new matter. All amendments have been done without prejudice, solely to facilitate the prosecution of the present application, and without acquiescence in any of the rejections. Applicants specifically retain the right to pursue subject matter within the full scope of the original claims in one or more continuing applications.

For the Examiner's convenience, in the following remarks and arguments, reference is made to the numbers used in the Office Action (Paper No. 14).

1. The Examiner withdrew Claim 20 from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species. Applicants respectfully traverse the withdrawal of Claim 20. Claim 1 has been amended to recite "a conjugate comprising an antibody Fab' fragment, covalently attached to a polyethylene glycol (PEG) molecule having an average molecular weight of at least 20 kD, wherein the apparent size of the conjugate is at least about 500 kD, and at least about 8 fold greater than the apparent size of the antibody fragment." Claim 20 recites, "The conjugate of Claim 1 wherein the PEG has an average molecular weight of at least about 40 kD." A PEG molecule having an average molecular weight of at least 40 kDa would qualify as being a member of a genus of PEG molecules having an average molecular weight of at least 20 kD. Since Claim 20 is within the scope of Claim 1 and Claim 20 is properly drawn to an elected species, the withdrawal of Claim 20 from further consideration is believed to be improper. Accordingly, the Examiner is respectfully requested to reunite Claim 20 with the rest of claims under examination.

2. Applicants note the New Grounds of Rejection set forth in the Office Action (Paper No. 14).

3. Applicants note the withdrawal of the objections and rejections with respect to cancelled Claims 5, 8, 10-19, 21, 24 and 30.

4. Applicants note that the petition filed under 37 CFR 1.84(a)(2) has been granted permitting the use of color drawings filed on November 29, 2000.

5. Applicants note that the Examiner has considered all the cited references in the Information Disclosure Statement as shown by the Examiner's initials on the copy of form PTO-1449.

6. The specification has been checked for incorrect ATCC address. Applicants note that the ATCC address on page 207, lines 8-9 was previously corrected (Paper No. 12). All other references to the address of ATCC have been corrected by the present amendment.

Rejections under 35 USC § 112, second paragraph

7-8. Claims 1, 25-26, 28-29 and 31-16 were rejected under 35 U.S.C. §112, second paragraph, as "being indefinite" in their recitation of the language "consisting essentially of."

Without acquiescing to the Examiner's position in the current rejection, and without prejudice to further prosecution of claims using the "consisting essentially of" transitional phrase in continuation or divisional applications, but, rather, in order to facilitate the expeditious prosecution of this application, Applicants have amended Claim 1 (and, as a consequence, those claims dependent from the same) to recite "comprising" instead of "consisting essentially of".

The support for the claim amendment can be found, at least, on page 26, lines 2-6 and page 28, line 3 of the specification, and original Claims 1, 5, 8, 13, 15, 16, 18, 19, 21 and 24. No new matter is believed to be added by the present claim amendments.

As the claims no longer recite the allegedly indefinite term, the withdrawal of the present rejection would be in order.

Rejections under 35 U.S.C. § 112, second paragraph

9. Applicants note the withdrawal of previous rejections with respect to Claims 1, 5, 8, 10-19, 21, 26 and 28-35.

R jections under 35 USC §§ 102 and 103

10-12. Claims 1, 25-26, 28-29 and 31-36 were rejected under U.S.C. 102(e) as being anticipated by Gonzalez et al. (U.S. Patent No. 6,133,426, of record, and U.S. Patent No. 6,025,158, of record). The attached Declaration under 37 CFR § 1.132 by Leonard Presta and Steven Leong, which were first submitted in parallel application Serial No. 09/234,182 establish that the cited patents are not "by another." Accordingly, the withdrawal of the present rejection would be in order.

13-14. Claims 1, 25, 31-33 and 36 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Zapata et al. (FASEB J. 1995, Abstract $128, 9:A1479, IDS #98) in view of Braxton (US Pat. No. 5,766,897, IDS #20).

The Zapata *et al.* poster presentation (IDS #97) teaches that the non-specific clearance of an antibody Fab fragment with a molecular weight of 49 kD can be decreased as much as 6-fold by the site-directed addition of a 10 kD PEG moiety. It further teaches that as long as the effective molecular size is *below* 70 kD, clearance decreases as molecular weight increases. (Citing Knauf, *J. Biol. Chem.* 263: 15064-15070, IDS #70).

The Examiner states that both Zapata *et al.* and Knauf *et al.* acknowledge that glomerular filtration is not the only mechanism of clearance which can be reduced by PEGylation proteins. Therefore, the Examiner alleges that in view of Braxton *et al.*, the ordinary artisan would have been motivated to use higher molecular weight PEGs for covalent linkage to any Fab' antibody fragments to further reduce the serum clearance of a therapeutic antibody.

Applicants respectfully point out to the Examiner that the art was unpredictable at the time of Applicants' invention. MPEP §2143.02 states, "Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness.... Whether an art is predictable ... is determined at the time the invention was made."

Because from the facts derived from the references, as set forth below, the art was unpredictable at the time the invention was made and there was no reasonable expectation of success in modifying or combining the references, the rejection is unsupported by the art and should be withdrawn.

Knauf *et al.* teaches that the *in vivo* clearance rate of an PEG-rIL conjugate rapidly decreases as the effective molecular size increases from 21 to approximately 70 kD, but above 70 kD clearance rate decreases much more slowly. Knauf *et al.* observed no further decrease in clearance rates when the apparent molecular weight of the protein was increased above 200 kD. Therefore, Knauf *et al.* predicted that a larger size of the conjugate corresponded to a slower clearance rate and that the hydrodynamic radius of the modified species governed the plasma clearance of the rIL-2. (See page 15068, right column, first full paragraph). Furthermore, Knauf *et al.* teaches that the authors were able to predict the systemic clearance rates of the molecules based on the hydrodynamic radii of the molecules. (See page 15068, left column, first partial paragraph).

Knauf *et al.* also states that "[p]lasma clearance of unmodified rIL-2 is comparable to that predicted for small protein which are cleared by *glomerular filtration in the kidney*....This relationship between the systemic clearance rate of rIL-2 species and hydrodynamic radius of the protein up to 70 kDa is consistent with the postulate that the *kidney is the major organ for clearance of all these molecules*." Accordingly, "[t]he *kidney* is therefore responsible for a *major* portion of the plasma clearance of *both* rIL-2 and *PEG-rIL-2*." (See page 15068, left column, first full paragraph and second paragraph; right column, first partial paragraph, emphasis added). In addition, Knauf *et al.* states that "[t]he rapid decrease in systemic clearance of PEG-rIL-2 as the effective molecular size increases from 21 to approximately 70 kDa, is *most likely due to a progressive exclusion of the protein from glomerular filtration*." (See page 15068, right column, second paragraph, emphasis added).

Therefore, the teaching of Knauf *et al.* indicating the increase in the size of the PEG results in a further reduction of the clearance rate is *clearly based on the*

assumption that the clearance mechanism of the glomerular filtration in the kidney is responsible for a major portion of the clearance of PEGylated proteins. As shown on Figure 9 of the Knauf *et al.*, there is no significant decrease in clearance rate once the apparent molecular weight of the protein reaches 70 kD, and there is no further decrease in clearance rates when the apparent molecular weight of the protein is increased above 200 kD.

Knauf *et al.* and Zapata *et al.*, when read alone or in combination, do not teach or suggest any other clearance mechanism which would be involved in the significant decrease of clearance rate of molecules with apparent molecular size greater than 70 kD. In view of Knauf *et al.*'s teaching, one could not extrapolate from Zapata *et al.*'s data, which were obtained with less than 70 kD antibody-PEG conjugates, that the clearance of antibody-PEG conjugates with an apparent molecular weight of at least about 500 kD would be reduced significantly.

Accordingly, even if Zapata *et al.* and Knauf *et al.* acknowledged that glomerular filtration is not the only mechanism of clearance which can be reduced by PEGylation of protein, based on their teachings, a person skilled in the art would not have been motivated to make and use antibody-PEG conjugates with apparent molecular weight of at least about 500 kD, and would not have reasonably expected any significant added benefit from increasing the molecular weight.

Similarly, Braxton *et al.* states, "Most proteins, particularly relatively low molecular weight proteins introduced into the circulation, are cleared quickly from the mammalian subject by the *kidneys*." (See column 1, lines 49-52, emphasis added). Braxton *et al.* also does not teach or suggest any other clearance mechanism which would result in a further reduction of the clearance rate by the conjugates with apparent molecular weight of at least 500 kD. Therefore, Braxton *et al.* has no teaching that would make up for the deficiency of the primary reference.

Consequently, in view of the teachings by Zapata *et al.*, Knauf *et. al.* and Braxton *et al.*, formulating such a conjugate would have offered no significant added benefits over conjugates of smaller size, which are below the glomerular cutoff size. If

there were other clearance mechanisms which would have resulted in a further significant reduction of the clearance rate by the conjugates with apparent molecular weight of at least 500 kD, they were not known or adequately disclosed in the cited art.

"Combining prior art references without evidence of such a suggestion, teaching or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability – the essence of hindsight." *In re Dembiczak*, 175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999).

Applicants respectfully submit that Zapata *et al.*, Knauf *et. al.* or Braxton *et al.* provides no suggestion or motivation to combine with any other reference or with knowledge available to one of ordinary skill in the art to make and use antibody-PEG conjugates with apparent molecular weight of at least about 500 kD. It is only the present invention that provides such link, and, of course, such hindsight reconstruction of an invention is legally impermissible.

Applicants also respectfully submit that based on the teachings of Zapata *et al.*, Knauf *et. al.* or Braxton *et al.*, it would not have been obvious to one of ordinary skill in the art to try to make and use antibody-PEG conjugates with apparent molecular weight of at least about 500 kD at the time it was made without the benefit of hindsight. However, even if it would have been obvious to try to make and use antibody-PEG conjugates with apparent molecular weight of at least about 500 kD, "obvious to try" is not a correct standard under §103. "'[O]bvious to try' is not the standard under § 103." *In re O'Farrell*, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988); *also see Ecolochem, Inc. v. Southern California Edison Co.*, 227 F.3d 1361, 56 USPQ2d 1065 (Fed. Cir. 2000).

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection as it applies to the claims pending.

15. Claims 26 and 28 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Zapata *et al.* in view of Braxton *et al.*, and in further view of Doerschuk *et al.* (US Patent No. 5,602,946, IDS #18). Zapata *et al.* and Braxton *et al.* were cited as discussed above, Doerschuk *et al.* was cited for its disclosure of anti-IL-8

antibodies, their humanized Fab' fragments, and other disclosure related to anti-IL-8 antibodies.

As discussed in response to the previous rejection, the combination of Zapata *et al.* and Braxton *et al.* does not make obvious the claims on which Claims 26 and 28 depend. Since Doerschuk *et al.* does not make up for the deficiencies of the primary combination, Claims 26 and 28 are not obvious for the same reasons as the base claims on which they depend. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

16. Claims 34 and 35 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Zapata *et al.* in view of Braxton *et al.*, and in further view of Griffith *et al.* (US Patent No. 5,670,132, IDS #13). Zapata *et al.* and Braxton *et al.* were cited as discussed above, Griffith *et al.* was cited for teaching the radiolabeling of a Fab'-PEG conjugate.

In response to the previous rejection, the combination of Zapata *et al.* and Braxton *et al.* does not make obvious the claims on which Claims 34 and 35 depend. Since Griffith *et al.* does not make up for the deficiencies of the primary combination, Claims 34 and 35 are not obvious for the same reasons as the base claims on which they depend. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Provisional obviousness-type double patenting rejection

Claims 1 25-26, 28-29 and 31-36 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1, 5, 10-13, 15-19, 21, 24-26 and 28-34 of co-pending Application No. 09/355,014. The attached Terminal Disclaimer is believed to overcome this rejection, the withdrawal of which is respectfully requested.

All claims pending in this application are believed to be in prima facie condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any fees, including any additional fees for extension of time, or credit overpayment to Deposit Account No. **08-1641** (Attorney's Docket No. **39766-0093C1**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: July 23, 2003

By: _____
Ginger R. Dreger (Reg. No. 33,055)

HELLER EHRMAN WHITE & McAULIFFE LLP
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

SV 446194 v1
7/23/03 9:55 AM (39766.0093)